

CLAIMS

What is claimed is:

1. A contrast agent for diagnostic imaging comprising vesicles which comprise a lipid, protein or polymer encapsulating a fluorinated gas, in combination with a targeting ligand, wherein said targeting ligand targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein GPIIb/IIIa receptor and said fluorinated gas is selected from the group consisting of a perfluorocarbon and sulfur hexafluoride.
2. A contrast agent according to Claim 1 wherein said vesicles comprise lipid vesicles.
3. A contrast agent according to Claim 2 wherein said lipid vesicles are selected from the group consisting of micelles and liposomes.
4. A contrast agent according to Claim 2 wherein said lipid comprises a phospholipid.
5. A contrast agent according to Claim 4 wherein said phospholipid is selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine and phosphatidic acid.
6. A contrast agent according to Claim 5 wherein said phosphatidylcholine is selected from the group consisting of dioleoylphosphatidylcholine, dimyristoylphosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidylcholine.
7. A contrast agent according to Claim 6 wherein said phosphatidylcholine comprises dipalmitoylphosphatidylcholine.
8. A contrast agent according to Claim 6 wherein said phosphatidylethanolamine is selected from the group consisting of dipalmitoyl-

phosphatidylethanolamine, dioleoylphosphatidylethanolamine, N-succinyldioleoylphosphatidylethanolamine and 1-hexadecyl-2-palmitoylglycerophosphoethanolamine.

9. A contrast agent according to Claim 8 wherein said phosphatidylethanolamine comprises dipalmitoylphosphatidylethanolamine.

5 10. A contrast agent according to Claim 5 wherein said phosphatidic acid comprises dipalmitoylphosphatidic acid.

11. A contrast agent according to Claim 2 wherein said lipid further comprises a polymer.

10 12. A contrast agent according to Claim 11 wherein said polymer comprises a hydrophilic polymer.

13. A contrast agent according to Claim 12 wherein said polymer comprises polyethylene glycol.

14. A contrast agent according to Claim 1 wherein said vesicles comprise protein vesicles.

15 15. A contrast agent according to Claim 14 wherein said protein comprises albumin.

16. A contrast agent according to Claim 1 wherein said vesicles comprise polymer vesicles.

20 17. A contrast agent according to Claim 16 wherein said polymer comprises synthetic polymers or copolymers which are prepared from monomers selected from the group consisting of acrylic acid, methacrylic acid, ethyleneimine, crotonic acid, acrylamide, ethyl acrylate, methyl methacrylate, 2-hydroxyethyl methacrylate, lactic acid, glycolic acid, ε-caprolactone, acrolein, cyanoacrylate, bisphenol A, epichlorhydrin, hydroxyalkylacrylates, siloxane, dimethylsiloxane, ethylene oxide, propylene oxide,

ethylene glycol, hydroxyalkylmethacrylates, N-substituted acrylamides, N-substituted methacrylamides, N-vinyl-2-pyrrolidone, 2,4-pentadiene-1-ol, vinyl acetate, acrylonitrile, styrene, p-amino-styrene, p-aminobenzylstyrene, sodium styrene sulfonate, sodium 2-sulfoxyethyl-methacrylate, vinyl pyridine, aminoethyl methacrylates and 2-methacryloyloxytrimethyl-ammonium chloride.

18. A contrast agent according to Claim 16 wherein said polymer comprises synthetic polymers or copolymers selected from the group consisting of polyacrylic acid, polyethyleneimine, polymethacrylic acid, polymethylmethacrylate, polysiloxane, polydimethylsiloxane, polylactic acid, poly(ϵ -caprolactone), epoxy resin, poly(ethylene oxide), poly(propylene oxide), poly(ethylene glycol), polyamide, polyvinylidene-polyacrylonitrile, polyvinylidene-polyacrylonitrile-polymethylmethacrylate and polystyrene-polyacrylonitrile.

19. A contrast agent according to Claim 18 wherein said polymer comprises polyvinylidene-polyacrylonitrile copolymer.

20. A contrast agent according to Claim 1 wherein said fluorinated gas comprises a perfluorocarbon.

21. A contrast agent according to Claim 20 wherein said perfluorocarbon gas is selected from the group consisting of perfluoromethane, perfluoroethane, perfluoropropane, perfluorobutane and perfluorocyclobutane.

22. A contrast agent according to Claim 21 wherein said perfluorocarbon gas is selected from the group consisting of perfluoropropane and perfluorobutane.

23. A contrast agent according to Claim 22 wherein said perfluorocarbon gas comprises perfluorobutane.

24. A contrast agent according to Claim 1 wherein said gas is derived, at least in part, from a gaseous precursor.

25. A contrast agent according to Claim 24 wherein said gaseous precursor has a boiling point of greater than about 37°C.
26. A contrast agent according to Claim 24 wherein said gaseous precursor comprises a perfluorocarbon.
- 5 27. A contrast agent according to Claim 26 wherein said perfluorocarbon is selected from the group consisting of perfluoropentane and perfluorohexane.
- 10 28. A contrast agent according to Claim 1 wherein said targeting ligand is selected from the group consisting of proteins, peptides, saccharides, steroids, steroid analogs, bioactive agents and genetic material.
29. A contrast agent according to Claim 28 wherein said targeting ligand is selected from the group consisting of proteins, peptides and saccharides.
30. A contrast agent according to Claim 29 wherein said targeting ligand is selected from the group consisting of proteins and peptides.
- 15 31. A contrast agent according to Claim 30 wherein said targeting ligand comprises a peptide.
32. A contrast agent according to Claim 31 wherein said peptide comprises a sequence selected from the group consisting of Arg-Gly-Asp and Lys-Gln-Ala-Gly-Asp-Val.
- 20 33. A targeted vesicle composition comprising vesicles which comprise a lipid, protein or polymer encapsulating a fluorinated gas, in combination with a targeting ligand, wherein said targeting ligand targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein GPIIb/IIIa receptor and said fluorinated gas is selected from the group
- 25 consisting of a perfluorocarbon and sulfur hexafluoride.

34. A targeted vesicle composition according to Claim 33 which targets regions of arteriosclerosis.

35. A targeted vesicle composition according to Claim 34 wherein said arteriosclerosis comprises atherosclerotic plaque.

5 36. A targeted vesicle composition according to Claim 33 which targets infarcted myocardium.

37. A targeted vesicle composition according to Claim 33 which targets cancer cells.

10 38. A targeted vesicle composition according to Claim 33 wherein said vesicles comprise lipid vesicles.

39. A targeted vesicle composition according to Claim 38 wherein said lipid comprises a phospholipid.

15 40. A targeted vesicle composition according to Claim 40 wherein said phospholipid is selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine and phosphatidic acid.

41. A targeted vesicle composition according to Claim 40 wherein said phosphatidylcholine is selected from the group consisting of dioleoylphosphatidylcholine, dimyristoylphosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidylcholine.

20 42. A targeted vesicle composition according to Claim 41 wherein said phosphatidylcholine comprises dipalmitoylphosphatidylcholine.

43. A targeted vesicle composition according to Claim 40 wherein said phosphatidylethanolamine is selected from the group consisting of dipalmitoyl-

phosphatidylethanolamine, dioleoylphosphatidylethanolamine, N-succinyldioleoyl-phosphatidylethanolamine and 1-hexadecyl-2-palmitoylglycerophosphoethanolamine.

44. A targeted vesicle composition according to Claim 43 wherein said phosphatidylethanolamine comprises dipalmitoylphosphatidylethanolamine.

5 45. A targeted vesicle composition according to Claim 40 wherein said phosphatidic acid comprises dipalmitoylphosphatidic acid.

46. A targeted vesicle composition according to Claim 38 wherein said lipid further comprises a polymer.

10 47. A targeted vesicle composition according to Claim 46 wherein said polymer comprises a hydrophilic polymer.

48. A targeted vesicle composition according to Claim 47 wherein said hydrophilic polymer comprises polyethylene glycol.

49. A targeted vesicle composition according to Claim 33 wherein said vesicles comprise protein vesicles.

15 50. A targeted vesicle composition according to Claim 49 wherein said protein comprises albumin.

51. A targeted vesicle composition according to Claim 33 wherein said vesicles comprise polymer vesicles.

20 52. A targeted vesicle composition according to Claim 51 wherein said polymer comprises synthetic polymers or copolymers which are prepared from monomers selected from the group consisting of acrylic acid, methacrylic acid, ethyleneimine, crotonic acid, acrylamide, ethyl acrylate, methyl methacrylate, 2-hydroxyethyl methacrylate, lactic acid, glycolic acid, ε-caprolactone, acrolein, cyanoacrylate, bisphenol A, epichlorhydrin, hydroxyalkylacrylates, siloxane, dimethylsiloxane, propylene oxide,

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ethylene oxide, ethylene glycol, hydroxyalkyl-methacrylates, N-substituted acrylamides, N-substituted methacrylamides, N-vinyl-2-pyrrolidone, 2,4-pentadiene-1-ol, vinyl acetate, acrylonitrile, styrene, p-amino-styrene, p-aminobenzylstyrene, sodium styrene sulfonate, sodium 2-sulfoxyethyl-methacrylate, vinyl pyridine, aminoethyl methacrylates and 2-methacryloyloxytrimethyl-ammonium chloride.

53. A targeted vesicle composition according to Claim 51 wherein said polymer comprises synthetic polymers or copolymers selected from the group consisting of polyacrylic acid, polyethyleneimine, polymethacrylic acid, polymethylmethacrylate, polysiloxane, polydimethylsiloxane, polylactic acid, poly(ϵ -caprolactone), epoxy resin, poly(ethylene oxide), poly(propylene oxide), poly(ethylene glycol), polyamide, polyvinylidene-polyacrylonitrile, polyvinylidene-polyacrylonitrile-polymethyl-methacrylate and polystyrene-polyacrylonitrile.

54. A targeted vesicle composition according to Claim 53 wherein said polymer comprises polyvinylidene-polyacrylonitrile copolymer.

55. A targeted vesicle composition according to Claim 33 wherein said fluorinated gas comprises a perfluorocarbon.

56. A targeted vesicle composition according to Claim 55 wherein said perfluorocarbon gas is selected from the group consisting of perfluoromethane, perfluoroethane, perfluoropropane, perfluorobutane and perfluorocyclobutane.

57. A targeted vesicle composition according to Claim 56 wherein said perfluorocarbon gas is selected from the group consisting of perfluoropropane and perfluorobutane.

58. A targeted vesicle composition according to Claim 57 wherein said perfluorocarbon comprises perfluorobutane.

59. A targeted vesicle composition according to Claim 33 wherein said targeting ligand is selected from the group consisting of proteins, peptides, saccharides, steroids, steroid analogs, bioactive agents and genetic material.

60. A targeted vesicle composition according to Claim 59 wherein said
5 targeting ligand is selected from the group consisting of proteins, peptides and saccharides.

61. A targeted vesicle composition according to Claim 60 wherein said targeting ligand is selected from the group consisting of proteins and peptides.

62. A targeted vesicle composition according to Claim 61 wherein said targeting ligand comprises a peptide.

63. A targeted vesicle composition according to Claim 62 wherein said
10 peptide comprises a sequence selected from the group consisting of Arg-Gly-Asp and Lys-Gln-Ala-Gly-Asp-Val.

64. A targeted vesicle composition according to Claim 33 wherein said targeting ligand is associated with said lipid, protein or polymer covalently.

65. A targeted vesicle composition according to Claim 33 wherein said
15 targeting ligand is unbound.

66. A targeted vesicle composition according to Claim 65 wherein said targeting ligand is associated with said lipid, protein or polymer non-covalently.

67. A targeted vesicle composition according to Claim 64 wherein said
20 covalent association comprises a covalent bond selected from the group consisting of amide, thioamide, ether, ester, thioester, -O-, -S-, -S_n-, where n is greater than 1, carbamate, -NH-, -NR-, where R is alkyl of from 1 to about 4 carbons, urethane, and substituted imidate bonds.

68. A targeted vesicle composition according to Claim 67 wherein said covalent association further comprises crosslinking.

69. A targeted vesicle composition according to Claim 64 wherein said targeting ligand is covalently associated with said lipid, protein or polymer via a linking
5 group.

70. A targeted vesicle composition according to Claim 69 wherein said linking group comprises a hydrophilic polymer.

71. A targeted vesicle composition according to Claim 70 wherein said hydrophilic polymer is selected from the group consisting of polyalkyleneoxides,
10 polyvinyl alcohol, polyvinylpyrrolidones, polyacrylamides, polymethacrylamides, polyphosphazenes, poly(hydroxyalkylcarboxylic acids) and polyoxazolidines.

72. A targeted vesicle composition according to Claim 71 wherein said hydrophilic polymer comprises a polyalkyleneoxide.

73. A targeted vesicle composition according to Claim 72 wherein said
15 polyalkyleneoxide is selected from the group consisting of polyethylene glycol and polypropylene glycol.

74. A targeted vesicle composition according to Claim 73 wherein said polyalkyleneoxide comprises polyethylene glycol.

75. A targeted vesicle composition comprising vesicles encapsulating a
20 fluorinated gas, in combination with a targeting ligand, wherein said targeting ligand targets tissues or receptors and said fluorinated gas is selected from the group consisting of perfluorocarbons and sulfur hexafluoride.

76. A targeted vesicle composition according to Claim 75 wherein said tissues are selected from the group consisting of myocardial tissue, membranous tissue,
25 lamina, interstitial tissue and tumors.

77. A targeted vesicle composition according to Claim 76 wherein said membranous tissue is selected from the group consisting of endothelium and epithelium.

78. A targeted vesicle composition according to Claim 75 wherein said receptors comprise the glycoprotein GPIIbIIIa receptor.

5 79. A targeted vesicle composition according to Claim 78 wherein said targeting ligand exhibits a binding affinity (K_d) to the GPIIbIIIa receptor of no greater than about 10^{-3} molar.

10 80. A targeted vesicle composition according to Claim 79 wherein said targeting ligand exhibits a binding affinity (K_d) to the GPIIbIIIa receptor of less than about 10^{-3} molar.

81. A targeted vesicle composition according to Claim 80 wherein said targeting ligand exhibits a binding affinity (K_d) to the GPIIbIIIa receptor of from about 10^{-9} molar to less than about 10^{-3} molar.

15 82. A targeted vesicle composition according to Claim 81 wherein said targeting ligand exhibits a binding affinity (K_d) to the GPIIbIIIa receptor of from about 10^{-7} molar to about 10^{-5} molar.

83. A targeted vesicle composition according to Claim 82 wherein said targeting ligand exhibits a binding affinity (K_d) to the GPIIbIIIa receptor of about 10^{-6} molar.

20 84. A targeted vesicle composition according to Claim 75 wherein said targeting ligand is selected from the group consisting of proteins, peptides, saccharides, steroids, steroid analogs, bioactive agents and genetic material.

85. A targeted vesicle composition according to Claim 84 wherein said targeting ligand is selected from the group consisting of proteins, peptides and saccharides.

86. A targeted vesicle composition according to Claim 85 wherein said targeting ligand is selected from the group consisting of proteins and peptides.

87. A targeted vesicle composition according to Claim 86 wherein said targeting ligand comprises a peptide.

5 88. A targeted vesicle composition according to Claim 87 wherein said peptide comprises a sequence selected from the group consisting of Arg-Gly-Asp and Lys-Gln-Ala-Gly-Asp-Val.

89. A targeted vesicle composition according to Claim 75 wherein said fluorinated gas comprises a perfluorocarbon.

10 90. A targeted vesicle composition according to Claim 89 wherein said perfluorocarbon gas is selected from the group consisting of perfluoromethane, perfluoroethane, perfluoropropane, perfluorobutane and perfluorocyclobutane.

15 91. A targeted vesicle composition according to Claim 90 wherein said perfluorocarbon gas is selected from the group consisting of perfluoropropane and perfluorobutane.

92. A targeted vesicle composition according to Claim 91 wherein said perfluorocarbon gas comprises perfluorobutane.

93. A targeted vesicle composition according to Claim 75 wherein said gas is derived, at least in part, from a gaseous precursor.

20 94. A targeted vesicle composition according to Claim 93 wherein said gaseous precursor has a boiling point of greater than about 37°C.

95. A targeted vesicle composition according to Claim 93 wherein said gaseous precursor comprises a perfluorocarbon.

96. A targeted vesicle composition according to Claim 95 wherein said perfluorocarbon is selected from the group consisting of perfluoropentane and perfluorohexane.

97. A targeted vesicle composition according to Claim 75 wherein said
5 targeting ligand is associated with said vesicles covalently.

98. A targeted vesicle composition according to Claim 75 wherein said targeting ligand is unbound.

99. A targeted composition according to Claim 98 wherein said targeting ligand is associated with said vesicle non-covalently.

100. A formulation for therapeutic or diagnostic use comprising, in
10 combination with a bioactive agent, lipid, protein or polymer vesicles encapsulating a fluorinated gas, in combination with a targeting ligand, wherein said targeting ligand targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein GPIIb/IIIa receptor and said
15 fluorinated gas is selected from the group consisting of perfluorocarbons and sulfur hexafluoride.

101. A formulation according to Claim 100 wherein said vesicles comprise lipid vesicles.

102. A formulation according to Claim 101 wherein said vesicles are
20 selected from the group consisting of micelles and liposomes.

103. A formulation according to Claim 100 wherein said gas is derived, at least in part, from a gaseous precursor.

104. A process for the preparation of a targeted vesicle composition which comprises lipid, polymer or protein vesicles encapsulating a fluorinated gas, in
25 combination with a targeting ligand, comprising combining together a lipid, protein or

Sub C1

Sub C2

polymer, a fluorinated gas and a targeting ligand, wherein said targeting ligand targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein GPIIbIIIa receptor and said fluorinated gas is selected from the group consisting of perfluorocarbons and sulfur hexafluoride.

5 105. A process according to Claim 99 wherein said targeting ligand and said lipid, protein or polymer are combined covalently.

106. A process according to Claim 104 wherein targeting ligand is combined with said lipid, protein or polymer in unbound form.

10 107. A process according to Claim 106 wherein said targeting ligand and said lipid, protein or polymer are combined non-covalently.

15 108. A process according to Claim 105 wherein said targeting ligand and said lipid, protein or polymer are combined together via a covalent bond which is selected from the group consisting of amide, thioamide, ether, ester, thioester, -O-, -S-, -S_n-, where n is greater than 1, carbamate, -NH-, -NR-, where R is alkyl of from 1 to about 4 carbons, urethane, and substituted imidate bonds.

109. A process according to Claim 105 wherein said targeting ligand and said lipid, protein or polymer are combined together via covalent crosslinking.

110. A process according to Claim 105 wherein said targeting ligand is combined covalently with said lipid, protein or polymer via a linking group.

20 111. A process according to Claim 110 wherein said linking group comprises a hydrophilic polymer.

112. A process according to Claim 111 wherein said hydrophilic polymer comprises polyethylene glycol.

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Sub C3

113. A process for the preparation of a formulation for diagnostic or therapeutic use which comprises, in combination with a bioactive agent, lipid, polymer or protein vesicles encapsulating a fluorinated gas, in combination with a targeting ligand, wherein the process comprises combining together said bioactive agent, lipid, protein or polymer, fluorinated gas and targeting ligand, wherein said targeting ligand targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein GPIIbIIIa receptor and said fluorinated gas is selected from the group consisting of perfluorocarbons and sulfur hexafluoride.

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Sub C4

114. A process according to Claim 113 wherein said vesicles comprise lipid vesicles.

115. A process according to Claim 114 wherein said lipids are selected from the group consisting of liposomes and micelles.

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Sub C4

116. A targeted vesicle composition comprising, in combination with a targeting ligand, lipid, polymer or protein vesicles encapsulating a fluorinated gas, wherein the targeted vesicle composition is prepared by combining together said lipid, protein or polymer, fluorinated gas and targeting ligand, wherein said targeting ligand targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein GPIIbIIIa receptor and said fluorinated gas is selected from the group consisting of perfluorocarbons and sulfur hexafluoride.

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Sub C4

117. A targeted vesicle composition according to Claim 116 wherein said vesicles comprise lipid vesicles.

118. A targeted vesicle composition according to Claim 117 wherein said vesicles are selected from the group consisting of liposomes and micelles.

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Sub C4

119. A targeted vesicle composition according to Claim 116 which targets regions of arteriosclerosis.

120. A targeted vesicle composition according to Claim 119 wherein said arteriosclerosis comprises atherosclerotic plaque.

121. A targeted vesicle composition according to Claim 116 which targets infarcted myocardium.

5 122. A targeted formulation for diagnostic or therapeutic use comprising, in combination with a bioactive agent, lipid, polymer or protein vesicles encapsulating a fluorinated gas, in combination with a targeting ligand, wherein the formulation is prepared by a process which comprises combining together said bioactive agent, lipid, protein or polymer, fluorinated gas and targeting ligand, wherein said targeting ligand targets cells or
10 receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein GPIIb/IIIa receptor and said fluorinated gas is selected from the group consisting of perfluorocarbons and sulfur hexafluoride.

123. A targeted formulation according to Claim 122 wherein said vesicles comprise lipid vesicles.

15 124. A targeted formulation according to Claim 123 wherein said lipid vesicles are selected from the group consisting of liposomes and micelles.

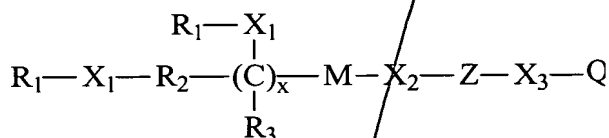
20 125. A method for providing an image of an internal region of a patient comprising (i) administering to the patient a targeted vesicle composition which comprises vesicles which comprise a lipid, protein or polymer encapsulating a fluorinated gas, in combination with a targeting ligand, wherein said targeting ligand targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein GPIIb/IIIa receptor and said fluorinated gas is selected from the group consisting of a perfluorocarbon and sulfur hexafluoride; and (ii) scanning the patient using ultrasound to obtain a visible image of the region.

25 126. A method for diagnosing the presence of diseased tissue in a patient comprising (i) administering to the patient a targeted vesicle composition which comprises vesicles which comprise a lipid, protein or polymer encapsulating a fluorinated gas, in

combination with a targeting ligand, wherein said targeting ligand targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein GPIIb/IIIa receptor and said fluorinated gas is selected from the group consisting of a perfluorocarbon and sulfur hexafluoride; and (ii) scanning the patient using ultrasound to obtain a visible image of any diseased tissue in the patient.

127. A method for the therapeutic delivery *in vivo* of a bioactive agent comprising administering to a patient a therapeutically effective amount of a formulation which comprises, in combination with a bioactive agent, lipid, protein or polymer vesicles encapsulating a fluorinated gas, in combination with a targeting ligand, wherein said targeting ligand targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein GPIIb/IIIa receptor and said fluorinated gas is selected from the group consisting of perfluorocarbons and sulfur hexafluoride.

128. A compound having the formula



wherein:

x is 0 or 1;

each X_1 is independently -O-, -S-, -SO-, -SO₂-, -NR₄-, -X₄-C(=X₅)-, -C(=X₅)-X₄- or -C(=X₅)-;

each X_2 and X_3 is independently a direct bond, -R₅-X₄-C(=X₅)-, -R₅-C(=X₅)-X₄-, -X₄-C(=X₅)-R₅-, -C(=X₅)-X₄-R₅-, -X₄-R₅-C(=X₅)-X₄-, -R₅-X₄-C(=X₅)-R₅-C(=X₅)-X₄- or -R₅-C(=X₅)-X₄-R₅-X₄-C(=X₅)-;

each X_4 is independently -O-, -NR₄- or -S-;

each X_5 is independently O or S;

M is a direct bond, -R₅-X₄-C(=X₅)-, -R₅-C(=X₅)-X₄-, -R₅-X₄-(YX₅)P(=X₅)-X₄- or -X₄-(YX₅)P(=X₅)-X₄-R₅-;

Y is hydrogen or a pharmaceutically acceptable counter ion;

5 Z is a direct bond or a hydrophilic polymer;
Q is a targeting ligand or a precursor thereto;
each R_1 is independently alkyl of 1 to about 50 carbons;
each R_2 is independently a direct bond or alkylene of 1 to about 30
carbons;
each R_3 and R_4 is independently hydrogen or alkyl of 1 to about 10
carbons; and
each R_5 is independently a direct bond or alkylene of 1 to about 30
carbons;
10 with the provisos that when three or more of X_1 , X_2 , X_3 , R_2 and M are direct bonds, then Z
is a hydrophilic polymer, and when Z is a direct bond, then three or more of X_1 , X_2 , X_3 , R_2
and M are other than direct bonds.

129. A compound according to Claim 128 wherein:
each X_1 is independently $-X_4-C(=X_5)-$, $-C(=X_5)-X_4-$ or $-C(=X_5)-$;
15 each of X_2 and X_3 is independently a direct bond, $-R_5-X_4-C(=X_5)-$,
 $-R_5-C(=X_5)-X_4$, $-X_4-C(=X_5)-R_5-$, $-C(=X_5)-X_4-R_5-$, $-X_4-R_5-C(=X_5)-X_4-$ or
 $-R_5-X_4-C(=X_5)-R_5-C(=X_5)-X_4-$;
each X_4 is independently $-O-$ or $-NR_4-$;
 X_5 is O; and
20 M is a direct bond, $-R_5-X_4-C(=X_5)-$ or $-R_5-X_4-(YX_5)P(=X_5)-X_4-$.

130. A compound according to Claim 129 wherein:
each X_1 is independently $-X_4-C(=X_5)-$ or $-C(=X_5)-X_4-$.

131. A compound according to Claim 132 wherein:
 X_1 is $-C(=X_5)-X_4-$.

132. A compound according to Claim 131 wherein:
each R_1 is independently alkyl of greater than 1 to about 40 carbons;
each R_2 is independently a direct bond or alkylene of 1 to about 20
25 carbons;
each of R_3 and R_4 is hydrogen or alkyl of 1 to about 5 carbons; and

each R₅ is independently a direct bond or alkylene of 1 to about 20 carbons.

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133. A compound according to Claim 132 wherein:
each R₁ is independently alkyl of about 5 to about 30 carbons;
each R₂ is independently a direct bond or alkylene of 1 to about 10 carbons;
each of R₃ and R₄ is hydrogen; and
each R₅ is independently a direct bond or alkylene of 1 to about 10 carbons.

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134. A compound according to Claim 133 wherein:
each R₁ is independently alkyl of about 10 to about 30 carbons;
each R₂ is independently a direct bond or alkylene of 1 to about 5 carbons; and
15 each R₅ is independently a direct bond or alkylene of 1 to about 5 carbons.

135. A compound according to Claim 134 wherein:
each R₁ is independently alkyl of from about 15 to about 28 carbons;
R₂ is a direct bond or -CH₂-; and
each R₅ is a direct bond or -(CH₂)_y-, where y is 1 or 2.

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136. A compound according to Claim 135 wherein Z is selected from the group consisting of a direct bond, polyalkyleneoxides, polyvinyl alcohol, polyvinylpyrrolidones, polyacrylamides, polymethacrylamides, polyphosphazenes, poly(hydroxyalkylcarboxylic acids) and polyoxazolidines.

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137. A compound according to Claim 136 wherein Z is selected from the group consisting of a direct bond and a polyalkyleneoxide.

138. A compound according to Claim 136 wherein said polyalkyleneoxide is selected from the group consisting of polyethylene glycol and polypropylene glycol.

139. A compound according to Claim 138 wherein said polyalkyleneoxide comprises polyethylene glycol.

140. A compound according to Claim 137 wherein Q comprises a targeting ligand.

141. A compound according to Claim 140 wherein said targeting ligand targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein GPIIb/IIIa receptor.

142. A compound according to Claim 141 wherein said targeting ligand is selected from the group consisting of proteins, peptides, saccharides, steroids, steroid analogs, bioactive agents, and genetic material.

143. A compound according to Claim 142 wherein said targeting ligand is selected from the group consisting of proteins, peptides and saccharides.

144. A compound according to Claim 143 wherein:

x is 1;

M is $-R_5-X_4-C(=X_5)-$; and

each of X_2 and X_3 is $-R_5-C(=X_5)-X_4$.

145. A compound according to Claim 144 wherein:

M is $-CH_2-O-C(=O)-$;

X_1 is $-C(=O)-O-$;

X_2 is $-CH_2CH_2C(=O)-NH-$;

X_3 is a direct bond, $-C(=O)-NH-$, $-HN-C(=O)-$, $-NH-C(=O)-CH_2$ or

$-NH-C(=O)-CH_2CH_2-$.

R_5 is alkyl of about 15 carbons;

R₂ is -CH₂-;
R₃ is hydrogen.

146. A compound according to Claim 145 wherein:
Q comprises a peptide.

5 147. A compound according to Claim 146 wherein:
Q comprises -Lys-Gln-Ala-Gly-Asp-Val or a cyclic peptide.

148. A compound according to Claim 145 wherein:
Q comprises a protein.

10 149. A compound according to Claim 148 wherein:
Q comprises Protein A.

150. A compound according to Claim 145 wherein:
Q comprises a saccharide.

151. A compound according to Claim 150 wherein:
Q comprises a monosaccharide.

15 152. A compound according to Claim 151 wherein:
Q comprises glucose.

153. A compound according to Claim 151 wherein:
Q comprises mannose.

20 154. A compound according to Claim 145 wherein:
Q comprises a precursor to a targeting ligand.

155. A compound according to Claim 154 wherein:
Q comprises a partially unsaturated or aromatic 5- to 7-membered
monocyclic ring containing 1 or 2 N, O or S atoms.

156. A compound according to Claim 155 wherein:
Q is selected from the group consisting of a maleimide moiety and a pyridyl moiety.
- 5 157. A compound according to Claim 143 wherein:
x is 1;
M is $-R_5-X_4-(YX_5)P(=X_5)-X_4-$; and
each of X_2 and X_3 is $-R_5-C(=X_5)-X_4$.
- 10 158. A compound according to Claim 157 wherein:
M is $-CH_2O-(HO)P(=O)-O-$ or $-CH_2O-(HO)P(=O)-NH-$;
 X_1 is $-C(=O)-O-$;
 X_2 is a direct bond $-CH_2CH_2NH-C(=O)-$ or
 $-CH_2CH_2NH-C(=O)-CH_2CH_2-(C=O)-NH-$;
 X_3 is a direct bond, $-C(=O)-NH-$, $-HN-(C=O)-$,
15 $-NH-C(=O)-CH_2CH_2-$ or $-(CH_2)_nC(=O)-NH$ where n is an integer from about 1 to about 10;
 R_1 is a straight chain alkyl of about 15 carbons;
 R_2 is $-CH_2-$; and
 R_3 is hydrogen.
- 20 159. A compound according to Claim 158 wherein:
Q comprises a peptide.
160. A compound according to Claim 159 wherein:
Q comprises $-Lys-Gln-Ala-Gly-Asp-Val$.
161. A compound according to Claim 158 wherein:
Q comprises a protein.
- 25 162. A compound according to Claim 161 wherein:
Q comprises Protein A.
163. A compound according to Claim 158 wherein:

Q comprises a precursor to a targeting ligand.

164. A compound according to Claim 163 wherein:

Q comprises a partially unsaturated or aromatic 5- to 7-membered monocyclic ring containing 1 or 2 N, O or S atoms.

5

165. A compound according to Claim 164 wherein:

Q is selected from the group consisting of a maleimide moiety and a pyridyl moiety.

10

166. A compound according to Claim 143 wherein:

x is 0;

M is a direct bond; and

each of X_2 and X_3 is a direct bond or $-R_5-C(=X_5)-X_4$.

15

167. A compound according to Claim 166 wherein:

X_1 is $-C(=O)-NH-$;

X_2 is a direct bond;

X_3 is $-C(=O)-NH-$;

R_1 is a straight chain alkyl of about 17 carbons or cholesterol; and

R_2 is a direct bond.

20

168. A compound according to Claim 167 wherein:

Q comprises a peptide.

169. A compound according to Claim 168 wherein:

Q comprises $-Lys-Gln-Ala-Gly-Asp-Val$.

170. A compound having the formula

L-P-T

wherein:

25

L is a hydrophobic compound;

P is a linking group; and

T is a targeting ligand.

171. A compound according to Claim 170 wherein L is a lipid.

172. A compound according to Claim 171 wherein said lipid is selected from the group consisting of lecithins, phosphatidylcholines, phosphatidylserines,
5 phosphatidylinositols, cardiolipins, cholesterol, cholesterolamines, lysophosphatides, erythro-sphingosines, sphingomyelins, ceramides, cerebroside, saturated phospholipids, unsaturated phospholipids, krill phospholipids and fatty acids.

173. A compound according to Claim 172 wherein said lipid is selected from the group consisting of lecithins, phosphatidylcholines, phosphatidylserines and
10 phosphatidylinositols.

174. A compound according to Claim 172 wherein said lipid is selected from the group consisting of 1,2-diacyl-sn-glycero-3-phosphocholines, 1,2-diacyl-sn-glycero-3-phosphoethanolamines, 1,2-diacyl-sn-glycero-3-[phospho-rac-(1-glycerols)], 1,2-diacyl-sn-glycero-3-phosphates, 1,2-diacyl-sn-glycero-3-
15 [phosphoserines], lysophosphatidylcholines, lysophosphatidylglycerols, 1,2-diacyl-sn-glycerols, 1,2-diacyl-ethylene glycols, N-(n-caproylamine)-1,2-diacyl-sn-glycero-3-phosphoethanolamines, N-dodecanylamine-1,2-diacyl-sn-glycero-3-phosphoethanolamines, N-succinyl-1,2-diacyl-sn-glycero-3-phosphoethanolamines, N-glutaryl-1,2-diacyl-sn-glycero-3-phosphoethanolamines, N-dodecanyl-
20 1,2-diacyl-sn-glycero-3-phosphoethanolamines, cholesterol and fatty acids.

175. A compound according to Claim 174 wherein said lipid is selected from the group consisting of 1,2-diacyl-sn-glycero-3-phosphocholines, 1,2-diacyl-sn-glycero-3-phosphoethanolamines, 1,2-diacyl-sn-glycero-3-[phospho-rac-(1-glycerols)], 1,2-diacyl-sn-glycero-3-phosphates, 1,2-diacyl-sn-glycero-3-
25 [phosphoserines], lysophosphatidylcholines, lysophosphatidylglycerols, 1,2-diacyl-sn-glycerols, cholesterol and fatty acids..

176. A compound according to Claim 170 wherein L is a protein.

177. A compound according to Claim 176 wherein said protein comprises albumin.

178. A compound according to Claim 170 wherein L is a polymer.

179. A compound according to Claim 170 wherein said polymer
5 comprises synthetic polymers or copolymers which are prepared from monomers selected from the group consisting of acrylic acid, methacrylic acid, ethyleneimine, crotonic acid, acrylamide, ethyl acrylate, methyl methacrylate, 2-hydroxyethyl methacrylate, lactic acid, glycolic acid, ϵ -caprolactone, acrolein, cyanoacrylate, bisphenol A, epichlorhydrin, hydroxyalkylacrylates, siloxane, dimethylsiloxane, ethylene oxide, propylene oxide,
10 ethylene glycol, hydroxyalkylmethacrylates, N-substituted acrylamides, N-substituted methacrylamides, N-vinyl-2-pyrrolidone, 2,4-pentadiene-1-ol, vinyl acetate, acrylonitrile, styrene, p-amino-styrene, p-aminobenzylstyrene, sodium styrene sulfonate, sodium 2-sulfoxyethyl-methacrylate, vinyl pyridine, aminoethyl methacrylates and 2-methacryloyloxytrimethyl-ammonium chloride.

180. A compound according to Claim 170 wherein said polymer
15 comprises synthetic polymers or copolymers selected from the group consisting of polyacrylic acid, polyethyleneimine, polymethacrylic acid, polymethylmethacrylate, polysiloxane, polydimethylsiloxane, polylactic acid, poly(ϵ -caprolactone), epoxy resin, poly(ethylene oxide), poly(propylene oxide), poly(ethylene glycol), polyamide,
20 polyvinylidene-polyacrylonitrile, polyvinylidene-polyacrylonitrile-polymethylmethacrylate and polystyrene-polyacrylonitrile.

181. A compound according to Claim 180 wherein said polymer comprises polyvinylidene-polyacrylonitrile copolymer.

182. A compound according to Claim 170 wherein said linking group
25 comprises a hydrophilic polymer.

183. A compound according to Claim 182 wherein said hydrophilic polymer is selected from the group consisting of polyalkyleneoxides, polyvinyl alcohol,

polyvinylpyrrolidones, polyacrylamides, polymethacrylamides, polyphosphazenes, poly(hydroxyalkylcarboxylic acids) and polyoxazolidines.

184. A compound according to Claim 183 wherein said hydrophilic polymer comprises a polyalkyleneoxide.

5 185. A compound according to Claim 184 wherein said polyalkyleneoxide is selected from the group consisting of polyethylene glycol and polypropylene glycol.

186. A compound according to Claim 185 wherein said polyalkyleneoxide comprises polyethylene glycol.

10 187. A compound according to Claim 170 wherein said targeting ligand targets cells or receptors selected from the group consisting of myocardial cells, endothelial cells, epithelial cells, tumor cells and the glycoprotein GPIIb/IIIa receptor.

15 188. A compound according to Claim 170 wherein said targeting ligand is selected from the group consisting of proteins, peptides, saccharides, steroids, steroid analogs, bioactive agents and genetic material.

189. A compound according to Claim 188 wherein said targeting ligand is selected from the group consisting of proteins, peptides and saccharides.

190. A compound according to Claim 187 wherein said targeting ligand targets regions of arteriosclerosis.

20 191. A compound according to Claim 190 wherein said arteriosclerosis comprises atherosclerotic plaque.

192. A compound according to Claim 187 wherein said targeting ligand targets infarcted myocardium.

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193. A compound according to Claim 187 wherein said targeting ligand targets cancer cells.

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